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The Preparation of Vicinal Difluoroolefinic Carbonyl Compounds and Their Application to the Synthesis of Difluororetinal Analogs[1]

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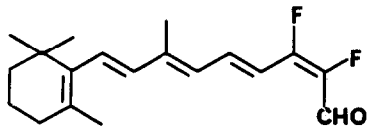
Abstract - The preparation of a novel vicinal difluorinated retinal analog is described. The key difluoroolefinic intermediate in the synthesis was prepared by the reaction of DAST with ethyl acetoacetate.

The modification of physiologically active biomolecules by selective fluorination is a well-established and frequently exploited technique. A large number of fluorinated retinoids have been prepared in our laboratories as well as others for vision chemistry,[2] bacteriorhodopsin[3] and epithelial skin cancer prevention studies.[4]

As part of our ongoing investigations of fluorinated retinal-containing proteins, the preparation of vicinally fluorinated retinal analogs 1 and 2 was a particularly intriguing challenge. Here, the strategic attachment of the magnetically active fluorine atoms onto the double bond which undergoes photochemically induced isomerization in bacteriorhodopsin[5] and rhodopsin could in principle be exploited by ^{19}F-NMR spectroscopy. In contrast to normal three-bond proton-proton coupling constants, vicinal olefinic difluorides, -FC=CF-, exhibit three-bond fluorine-fluorine coupling constants that are dramatically dependent upon the double bond configuration; i.e., $^{3}J_{FF}$ (cis) ≃ 0-20 Hz and $^{3}J_{FF}$ (trans) ≃ 120-140 Hz.[6] The relative magnitudes of these coupling constants renders configuration assignments completely unambiguous and would be especially advantageous for biomolecules wherein intrinsic line broadening is a serious drawback.

We now wish to report on a convenient procedure for the preparation of appropriately functionalized fluorinated intermediates useful for the construction of vicinal difluoropolyenes and, in particular, the synthesis of retinal analog 1. This straightforward synthetic protocol (SCHEME 1) featured the novel reaction of diethylaminosulfur trifluoride (DAST) with ethyl acetoacetate to provide the key difluorinated intermediate 3 as an E/Z mixture.[7]



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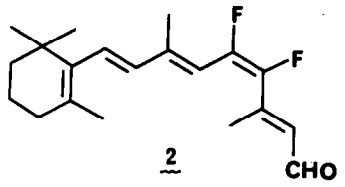

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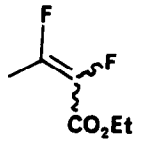

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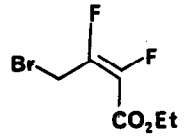

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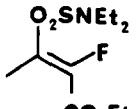
Somewhat fortuitously, the requisite ethyl (2Z)-4-bromo-2,3-difluoro-2-butenoate 4 was stereospecifically and regioselectively prepared by the Wohl-Ziegler bromination of the isomeric mixture of ethyl (2E/2Z)-2,3-difluoro-2-butanoate 3 (2E/2Z ~1). That the 2Z-isomer of 4 was the sole product in this reaction indicates a pronounced thermodynamic preference for this configurational form relative to the corresponding 2E-isomer.

The following experimental procedure illustrates the preparation of the relatively volatile difluoroesters 3 and, without isolation, their subsequent direct conversion to 4: In a typical preparation, a solution of ethyl acetoacetate (1.30g, 10.0 mmol) in 1-methyl-2-pyrrolidinone, NMP, (10 mL) was added by cannula to a stirred solution of DAST (3.55g, 22.0 mmol) in NMP (5 mL) at -70° under Ar. The reaction mixture was then stirred at RT for 48-64 h. After cooling, diluting with water (30 mL) and extracting with CCl_4 (25 mL total), the organic extract was dried ($MgSO_4$), filtered and vacuum distilled (T_{pot} < 40°, 0.1 torr).[8] To the resultant colorless distillate, a CCl_4 solution of isomeric esters 3, was added NBS (1.78g, 10.0 mmol) and Bz_2O_2 (~10 mg). After gently refluxing for 18 h, the mixture was worked up in the usual manner to give crude bromodifluoroester 4.[9] Vacuum distillation (T_{pot} < 50°, 0.1 torr) afforded pure 4[10] as a pale yellow oil in 48-58% overall yield (data from several runs).

The scope and generality of the reaction of DAST with several acyclic 1,3-dicarbonyl compounds was examined with the following results:

ethyl 3-oxooctanoate → ethyl (2E/2Z)-2,3-difluoro-2-octenoate
butyl acetoacetate → butyl (2E/2Z)-2,3-difluoro-2-butenoate, 6[10]
2,4-pentanedione → (3E/3Z)-3,4-difluoro-3-penten-2-one, 7[10]

In these examples, the resultant vicinal difluoroolefinic carbonyl compounds were also obtained as 1:1 isomeric mixtures in 40-60% overall yield. In addition, compounds 6 and 7 were subjected to NBS bromination according to the above procedure to provide their corresponding allylic bromo derivatives 8[10] and 9,[10] respectively.



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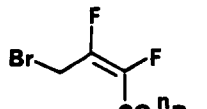

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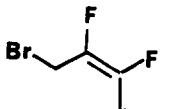

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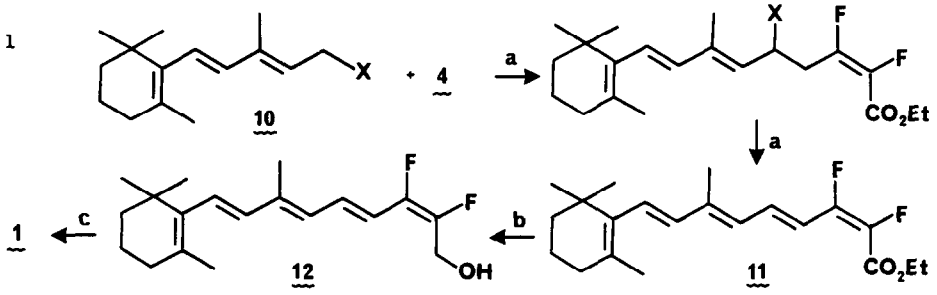
In contrast, ethyl benzoylacetate, dibenzoylmethane and conjugated ß-ketoesters afforded only minor amounts of the desired vicinal difluoroolefins.

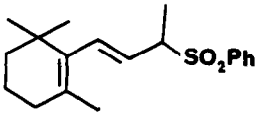
With the key intermediate 4 on hand, the elaboration of this compound to the difluororetinal analog 1 was readily effected by the alkylation of the lithium salt of C_{15}-sulfone 10 followed by the base-induced elimination of tolylsulfinic acid to afford the difluoroester 11.[10] Reduction of 11 with diisobutylaluminum hydride gave the difluororetinol analog 12[10] as the sole product. Lastly, MnO_2 oxidation gave the desired difluororetinal analog 1[10] in >90% isomeric purity together with minor amounts (<10%) of 13E-1 and an unidentified isomer.

SCHEME 1



a. LDA, THF, -78°; b. DIBAL, P.E., -78°; c. MnO_2 $(X = SO_2{}^{p}Tol)$

The direct preparation of difluoro C_{18}-ketone 15 from the reaction of C_{13}-sulfone 13 with bromodifluoroketone 9 was not successful. However, it was observed that 13 could be efficiently alkylated with 4 to provide the Z-difluorotetraenoate 14,[10] a useful intermediate for the anticipated preparation of the strategically fluorinated analog of 11-cis-retinal, (11Z)-11,12-difluororetinal 2.



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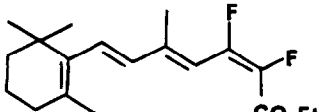

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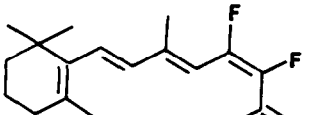

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Work currently in progress in our laboratories includes the completion of the synthesis of 2 as well as the formation of fluorinated analogs of rhodopsin and bacteriorhodopsin with 1 and 2. These results will be forthcoming in a future communication.

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2. (a) A. E. Asato, H. Matsumoto, M. Denny and R. S. H. Liu, J. Am. Chem. Soc., (1978), 100, 5957-5960; (b) R. S. H. Liu, H. Matsumoto, A. E. Asato, M. Denny, Y. Shichida, T. Yoshizawa and F. W. Dahlquist, J. Am. Chem. Soc., (1981), 103, 7195-7201.
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5. L. Packer, Ed., "Methods in Enzymology," Academic Press, New York, 1982, 88, Biomembranes, Part 1. Visual Pigments and Purple Membrane II.
6. J. W. Emsley, L. Phillips and V. Wray in "Fluorine Coupling Constants," 1977, Pergamon Press, pp. 115-116 and 421-446 (Table B.1.f).
7. We wish to express our gratitude to Dr. William J. Middleton for initially communicating to us his unreported results on the preparation of 3 from ethyl acetoacetate and DAST in a polar, aprotic medium. We are also indebted to Dr. George Boswell of E. I. duPont de Nemours & Company for providing us with valuable information regarding the chemistry of DAST with 1,3-dicarbonyl compounds. This work was supported by a grant from the U.S. Public Health Services (AM-17806).
8. The pot residue consisted of the sole by-product in this conversion and was tentatively identified as 5.[10]
9. In the early stages of the NBS bromination of isomeric 3 it was observed by ^{1}H-nmr spectroscopy that 2E-3 underwent efficient isomerization to 2Z-3 prior to significant accumulation of the final product, 4.
10. ^{19}F-NMR (80 MHz, $CDCl_3$, $CFCl_3$): 2Z-3 δ-100.7 (F_3, dq, J_d = 2.4 Hz, J_q = 19.6 Hz) and -154.6 (F_2, m) ppm; 2E-3 δ-118.0 (F_3,dq, J_d = 129.8 Hz, J_q = 17 Hz) and -166.3 (F_2, dq, J_d = 129.9 Hz, J_q = 5.9 Hz) ppm; 3Z-4 δ-113.4 (F_3, t, J = 24.0 Hz) and -146.2 (F_2, bs) ppm, $^{3}J_{FF} \simeq 0$ Hz; 5 δ-142.7 (F_2, d, J = 2.8 Hz) ppm; 2Z-6 δ-100.5 (F_3, q, J = 19.7 Hz) and -154.7 (F_2, bs) ppm ($^{3}J_{FF} \simeq 0$ Hz); 2E-6 δ-118.2 (F_3, dq, J_d = 129.0 Hz, J_q = 17.7 Hz) and -166.6 (F_2, dq, J_d = 129.5 Hz, J_q = 5.9 Hz); 2Z-7 δ-99.95 (F_4, q, J = 19.3 Hz) and -151.2 (F_3, m) ppm, $^{3}J_{FF} \simeq 0$ Hz; 2E-7 δ-118.7 (F_4, bd, J = 130 Hz) and -162.9 (F_3, bd, J = 128.5 Hz) ppm; 2Z-8 δ-113.8 (F_3, t, J = 24.6 Hz) and -146.0 (F_2, bs) ppm, $^{3}J_{FF} \simeq 0$ Hz; 3Z-9, δ-113.8 (F_4, t, J = 24.5 Hz) and -144.0 (F_3, bs) ppm, $^{3}J_{FF} \simeq 0$ Hz; 13Z-11 δ-127.0 (F_{13}, d, J = 26.2 Hz) and -152.3 (F_{14}, bs) ppm, $^{3}J_{FF} \simeq 0$ Hz; 13Z-12 δ-140.9 (F_{14}, dt, J_d = 9.3 Hz, J_t = 22.6 Hz) and -145.3 (F_{13}, dd, J = 9.3, and 26.0 Hz) ppm; 13Z-1 δ-123.3 (F_{13}, dd, J = 7.2, 27.2 Hz) and -157.2 (F_{14}, d, J= 9 Hz) ppm; 11Z-14 δ-116.3 (F_{11}, dm, J = 33.6 Hz) and -152.9 (F_2, bs) ppm, $^{3}J_{FF} \simeq 0$ Hz.
^{1}H-NMR (300 MHz, $CDCl_3$, TMS): 13Z-1 δ-1.04, 1.71, 2.07, 6.14 (H_8, d, J = 16.1 Hz), 6.24 (H_{10}, d, J = 12.3 Hz), 6.37 (H_7, bd, J = 16.6 Hz), 6.83 (H_{12}, dd, J = 14.9, 28.1 Hz) 7.31 (H_{11}, dd, J = 11.6, 15.0 Hz) and 9.70 (H_{15}, dd, J = 4.3, 10.3 Hz) ppm.

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